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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/067,448 | 02/05/2002 | David J. Emanuel | OC01392K | 7394 |

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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| EXAMINER | |
|---|---|
| CANELLA, KAREN A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/067,448 | EMANUEL ET AL. | |
| | Examiner | Art Unit | |
| | Karen A. Canella | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-3,8-10,14-16,19-21,24 and 25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3,8-10,14-16,19-21,24 and 25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 4-7, 11-13, 17, 18, 22 and 23 have been canceled. Claims 1, 2, 8-10, 14-16, 19-21, 24 and 25 have been amended. Claims 1-3, 8-10, 14-16, 19-21, 24 and 25 are pending and under consideration.

The rejection of claims 1-3, 8, 9, 14-16, 19-21 and 24 under 35 U.S.C. 103(a) as being unpatentable over Albanell and Baseiga, (Drugs of Today, 1999, Vol. 35, pp. 931-946) in view of Kastrup et al, Editor (Drug Facts and Comparisons, 1999, pp. 3447-3455) and Parahadadiopoulos et al (PNAS, 1991, Vol. 88, pp. 11460-11464) is maintained for reasons of record.

Claim 1 is drawn to a method of treating breast cancer, lung cancer, pancreatic cancer, colon cancer, myeloid leukemia, melanoma, thyroid follicular cancer, bladder carcinoma, glioma, myelodysplatic syndrome ovarian cancer or prostae cancer cmprising adminisntering to a pateint a theraeptucially effective amount of a liposomal anthracycline composition prior to, concurrently or after administration of Trastuzumab, wherein said liposomal anthracycline composition is pegylated liposomal doxorubicin comprising (a) doxorubicin HCl; (b) N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt; (c) fully hydrogenated soy phosphatidylcholine; (d) cholesterol; histidine, HCl and or NaOH, amonium sulfate and sucrose; wheein the weight percentage ratio of a:b:c:d is about 1.0: 1.60: 4.80: 1.60 mg/m;, respetively. Claim 2 embodies the method of claim 1 wherein said pateint is a treatment experienced pateint having a proliferative disease and/or has at least one cardiac risk factor and/or has had previous anthracycline therapy. Claim 3 embodies the method of claim 2 further comprising an additional antineoplastic agent. Claim 8 embodies the method of claim 2 wherein the pegylated liposomal anthracycline composition and Trstuzumab are administered sequentially. Claim 9 embodies the method of claim 2 wherein the pegylated liposomal anthracycline composition is administered first. Claim 14 embodies the method of claim 3 wheein the additonal antineoplastic agent is selected from the group consisting of uracil mustard, cyclophosphamide, ifosamide, melphalan, chloambucil, temozolomide, 5-FU, fludarabine phosphate, Gemcitabine, Paclitaxel, Docetaxel, Interferons, Etoposide, Tamoxifen, Leuprolide, Flutamide, Toremifene, cisplatin, Carboplatin, Navelbene, CPT-11, anastrazole,

Letrazole and Capecitabine. Claim 15 embodies the method of claim 3 wherein the pegylated liposomal composition, Trastuzumab and the additional antineoplastic agent are administered sequentially. Claim 16 embodies the method of claim 3 wherein the additional antineoplastic agent is cyclophosphamide. Claim 19 embodies the method of claim 1 wherein the pegylated liposomal anthracycline composition is administered in the amount of about 20 to about 50mg/m2, given over a time period of about 45 to about 90 minutes every three to four weeks. Claim 20 embodies the method of claim 1 wherein Trastuzumab is administered first in the amount of aobut 2 to about 6 mg/kg given once over a time period of about 60 to about 90 minutes and subsequently adminsitered in the amount of about 2 to 6 mg/kg given over a period of about 60 to 90 minutees every one to four weeks. Claim 21 embodies the mehod of claim 3 wherein the additoanl antineoplastic agent is administeed in the amount of about 400 to about 600 mg/m2 given over a period of about 20 to about 60 minutes every two to four weeks. Claim 24 embodies the method of claim 3 wherein the pegylated liposomal doxorubicin cmposition is adminsitered in the amount of about 20 to about 50 mg/m2 given over a period of about 45 minutes to about 90 minutes every three to four weeks; trastuzusamab is administerd first in the amount of about 2 to about 8 mg/kg given over a peiod of about 60 to about 90 minutes and subsequently administered in the amount of about 2 to about 8 mg/kg given over a peiod of about 60 to about 90 minutes every one to four weeks, and the additional antineoplastic agent is cyclophsophamide and is administered in the amount of about 400 to about 600 mg/m2 given over a period of about 20 to about 60 minutes every two to four weeks.

Albanell and Baseiga teach a method of treating breast cancer comprising the administration of the combination of docorubicin and cyclophosphamide to patinets not previously treated with doxorubicin, on a schedule of 60 mg/m2 doxorubicin plus 600 mg/m2 cyclophosphamide (page 941, second column, lines 6-7). Albanell and Baseiga teach that all chmotherpay regimens were administered once every three weeks (page 941, second column, lines 11-14). Albanell and Baseiga teach that half of the patients were then selected to receive Albanell and Baseiga in an initial 4 mg/kg loading followed by 2 mg/kg every week (page 941, second column, lines 15-19). Albanell and Baseiga teach that myocardial disfunction syndrome was more common in the combined treatment of doxorubicin, cyclophosphamide and trastuzusamab than with doxorubicin combined with cyclophosphamide (page 941, second

column, lines 24-27). Thus, Albanell and Baseiga teach the specific embodiemtns of all the instant claims with the exception of the adminsitration of liposomal doxorubicin rather than doxorubicin, the treatment of a patinet with a cardiac risk factor or previous anthrcycline therpy, the specific embodiemtns of claims 4 and 5, and the amount and time of administration of the pegylated anthracyclin in claims 19 and 24.

Kastrup et al (Drug Facts and Comparisons, 1999, pp. 3447-3455) teach that special attentaion must be given to cadiac toxicity in patients who have received total doses of doxorubicin exceeding the recommended amount of 550 mg/m2 and that dose-related incidents range to 20% for patients receiving doses of doxorubicin of greater than 700 mg/m2, and that the limit for patients receiveing radiotherapy to the mediastinal area, or other potentially cardiotoxic agents such as cyclophosphamide or daunorubicin, may be lower (page 3448, lines 10-17, under "Warnings"). Kastrup et al teach that because of the slower clearance of doxil relative to free doxorubicin, the AUC of liposomal doxorubicin is two to three orders of magnitude larger than the AUC for a similar dose of free doxorubicin (page 3448, lines 4-9 under the ehading "Doxorubicin HCL (ADR)"). Kastrup et al teach a recommended dose of 20 mg/m2 of doxorubicin in lipsomal formulation over 30 minutes, once every three weeks which fulfills the specific embodiemtn of claim 19.

Parahadadiopoulos et al teach sterically stabilized iposomes included in the formulation of PEG-liposomes exhibit prolonged circulation time in blood and clearance rates that are completely depdnent of dosage over a wide range (page 11460, second column, lines 6-10). Parahadadiopoulos et al teach that said liposomes produce a marked enhancement of antitumor activity of encaspulated doxorubicin and eptirubicin in mice against both lymphoma and coonc carcinoma cells, with a concomittent decrease intoxicity (page 11460, first column, lines 10-14). Parahadadiopoulos et al teach the sterically stabilizes liposomes have a therapetuic index which is much higher than that observed with conventional liposomes (page 11460, first column, lines 14-16). Parahadadiopoulos et al teach that marked ecrease in accumulation in the liver and spleen and a marked increase in accumulation in tumors (abstract, lines 9-11). Parahadadiopoulos et al teach the composition of liposomes made from ploye thelene glycol conjugated to disteroyl phosphatidyl ethanolamine, hydrogenated soy phsophatidyl choline, cholesterol and alpha tocopherol in molar ratio which is the same as the weight ratios of claims 5

and 6 (page 11461, first column, lines 18-24). Parahadadiopoulos et al teach that the lower acute toxicity of the anthracycline-loaded PEG-liposomes is due to the delayed clearance of the drug from the blood and the reduction of peak plasma levels of the free drug which adversely affects sensitiive non-target tissues such as the heart (page 11464, first column, lines 18-22).

It would have been prima facie obvious at the time the claimed invention was made to substitute an administration of 20 mg/m2 of doxorubicin in lipsomal formulation over 30 minutes, once every three weeks for the administration of 60 mg/m2 doxorubicin given once every three weeks in the combination chemotherapy as taught by Albanell and Baseiga. One of skill in the art would have been motivated to do so by the teachigns of Albanell and Baseiga on the increased inicidence of myocardial dysfunction observed in the combination therapy with doxorubicin, cyclophosphamide and trastuzusamab relative to the incidence of myocardial dysfunction observed in the combination of doxorubicin and cyclophosphamide without Trastuzusamab and the teachings of Parahadadiopoulos et al on the lower acute toxicity of anthracyclin-loaded PEG liposomes due to the reduction of peak plasma levels which reduces the adverse effects on non-taret tissues such as the heart, and the teachings of Kastrup et al on the increased therapic index of liposomal doxorubicin which is evident from the lower recommended dose relative to conventional doxorubicin (20 mg/m2 versus 60-75mg/m2, page 3450, "Administration and Dosage"). One of skill in the art would reasonably conclude that the combination of doxorubicin, cyclophosphamide and trastuzusamab is in of itself a cardiac risk factor. Further one of skill in the art would be motivated to decrease the risk of myocardial dyfunction both in patients previously exposed ot anthrcyclines and other chemotherpauic agnet s which cause cardio toxicity and in patinets who have not recived previous chemotherpy by lowering the total amount of doxorubicin which is administered (20mg/m2 versus 60mg/m2).

The rejection of Claims 1-25 under 35 U.S.C. 103(a) as being unpatentable over Albanell and Baseiga, (Drugs of Today, 1999, Vol. 35, pp. 931-946) and Kastrup et al, Editor (Drug Facts and Comparisons, 1999, pp. 3447-3455) and Parahadadiopoulos et al (PNAS, 1991, Vol. 88, pp. 11460-11464) as applied to claims 1-3, 8, 9, 14-16, 19-21 and 24 above and in further view of Waksal et al (US 2002/0012663) and the abstract of Hudis et al (J. Clin. Oncol., Jan 1999, Vol. 17, pp. 93-100) is maintained for reasons of record.

Claim 10 embodies the method of claim 2 wherein Trastuzusamab administered first. Claim 25 embodies the method of claim 24 wherein the pegylated liposomal dxorubicin composition is administered first followed by cyclophosphamide and the trastuzusamab. Albanell and Baseiga teach a method wherein doxorubcin is administered together with cycliphosphamide followed by trastuzusamab. None of the aforesaid references teaches the administration of doxorubicin follwed by cyclophosphamide, or the administration of trastuzusamab before the administration of the liposomal doxorubicin.

Waksal et al teach the administration of the EGFR/HER2 antibody before treatent with chemotherapeutic agnets (page 7, paragraph 0095, lines 6-10).

The abstract of Hudis et al teaches a chemotherpeutic regimen comprising the administration of cyclophosphamide after the administration of doxorubicin.

It would have been prima facie obvious to one of skill in the art at the time the invetion was made to optimize the tretment protocol by changing parameters known to be variable, such as the order of administration of drugs within a combination regimen. One of skill in the art would have been motivated to do so by the teachings of Waksal et al that the anti-HER2 antibody is administered before the chemotherpaic agent and the teachings of the abstract of Hudis et al which demonstrates that cyclophophamide need not be co-administered in the same infusion with doxorubicin.

Applicant argues that there is no motivation to combine the references to arrive at applicant's claimed invetion. Applicant argues that the Albanell et al reference has a 1999 publication date, but that the Parahadadiopoulos reference has a 1991 publication date. Applicant states that even though the secondary reference was avaible before the pirmary reference, the primary reference does not utilize the information found in the secodary reference. This has been considered but not found persuasive. In response to applicant's argument based upon the age of the references, contentions that the references is eight years older than one of the other references is not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See In re Wright, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
5/31/2005

KAREN A. CANELLA PH.D
PRIMARY EXAMINER